PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 August 1998 (12.08.98)	
International application No. PCT/CA98/00015	**Applicant's or agent's file reference** 8844-8/PAR
International filing date (day/month/year) 12 January 1998 (12.01.98)	**Priority date** (day/month/year) 10 January 1997 (10.01.97)
Applicant DELOVITCH, Terry, L.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

23 July 1998 (23.07.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Catherine Massetti
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
8844-8/PAR		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00015	12/01/1998	10/01/1997
International Patent Classification (IPC) or national classification and IPC A61K38/17		
Applicant THE JOHN P. ROBARTS RESEARCH INSTITUTE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/07/1998	29.04.99
Name and mailing addr ss of the int rnational preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. (+31-70) 340-2040 Tx: 31 651 epo nl Fax: (+31-70) 340-3016	Authorized officer Fernandez y Branas,F Telephone No. (+31-70)-340

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00015

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-32 as originally filed

Claims, No.:

1-31 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Th questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-16.

because:

☒ the said international application, or the said claims Nos. 1-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	17-31
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	17-31
Industrial applicability (IA)	Yes:	Claims	1-31 (See Sep. Sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-16 relate to a method of treatment of the human or animal body by therapy in the sense of Article 34(4)(a)(i) and Rule 67.1(iv) PCT.

The IPEA will nevertheless give an opinion on the novelty and inventive step of the subject matter of claims 1-16 as if they were drafted in a manner not falling within the meaning of Article 34(4)(a)(i) and Rule 67.1(iv) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1.....WO-A-9005541 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN)
D2.....WO-A-9319767 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN)
D3.....WO-A-9505464 (ARCH DEVELOPMENT CORPORATION)
D4.....WO-A-9503408 (DANA-FARBER CANCER INSTITUTE/ REPLIGEN CORP.)
D5.....Immunity, Vol 5, 1996, pages 285-293

1) For the assessment of the presently worded claims 1-31 on the question whether their subject matter is industrially applicable, no unified criteria exist in the PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, for example, does not recognise the subject matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for first medical use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical

treatment.

2) In the case of a known substance or composition, this may only be patented for use in methods of treatment of the human or animal body if the known substance or composition was not previously disclosed for use in therapy ("first medical use"). The same substance or composition cannot subsequently be patented for any other use of that kind.

3)D1 discloses pharmaceutical compositions comprising anti CD28 agonist antibodies, see for example claims 12-32; see also D2, page 5 line 20 to page 10 line 30; pharmaceutical compositions comprising the B7-2 polypeptide are also known in the art, see D3, page 52, lines 20-32; see also D4, page 57 line 9 to page 58 line 37 and claim 170.

4) Thus, in view of any of D1-D2 and bearing in mind point 2) above the subject matter of claims 17-21, 23-29 and 31 lacks novelty in the sense of Article 33(2) PCT. In view of any of D3-D4 the subject matter of claims 17-19, 22-27 and 30-31 lacks novelty in the sense of Article 33(2) PCT.

5) In view of the prior art the subject matter of claims 1-16 appears to be new according to Article 33(2) PCT.

6) For the analysis of the inventive step of the subject matter of claims 1-16 D5 is considered to be the closest prior art. D5 discloses that administration of CTLA-4Ig or anti-B7-2 mAbs blocked diabetes in nonobese diabetic mouse (NOD), when administered to mice between 5 and 7 weeks of age. CTLA-4Ig Tg^+ NOD mice and $CD28^{-/-}$ NOD mice displayed a more rapid onset and severity of diabetes . In the later animals, disruption of the CD28/B7 interaction contributed to the exacerbation of the autoimmune disease, see first page, right column. It is concluded that the CD28 signalling pathway controls the development of autoimmune diabetes in NOD mouse by

regulating the balance Th1/ Th2 subsets. The blockade of CD28/B7 during the early phase of the T-cell activation contributes to an increase incidence of the disease, see page 290, right column.

The difference between the present application and D5 is that in the present application agonists of the CD28 receptor (e.g. anti CD28 antibodies or the B7-2 polypeptide) is used in the preparation of medicaments for preventing the development of autoimmune disease. In view of this difference the problem to be solved by the present application can be defined as the provision of alternative medicaments for preventing autoimmune diseases.

Although D5 mentions that disruption of the CD28/B7 interaction contributes to the development of the disease, no clear suggestion can be found in D5 directing the skilled person to the stimulation of the CD28 receptor with costimulatory agonist compounds. Thus, the subject matter of claims 1-16 involves an inventive step in the sense of Article 33(3) PCT.

Re Item VIII

Certain observations on the international application

The subject matter of claims 10-16 is not considered to be supported by the description. No evidence is provided in the present application to show that the claimed methods would work in prolonging acceptance of engrafted tissue (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
8844-8/PAR		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 98/00015	12/01/1998	10/01/1997
Applicant		
THE JOHN P. ROBARTS RESEARCH INSTITUTE et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 3
   - [X] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 98/00015

Box I Observation where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 1-16
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the
alleged effects of the compound.

INTERNATIONAL SEARCH REPORT

Interr[redacted]l Application No
PCT/CA 98/00015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/17 A61K39/395 //C07K14/705,16/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 90 05541 A (UNIV MICHIGAN ;SQUIBB BRISTOL MYERS CO (US)) 31 May 1990 see claims 12-32 ---	17-21, 23-29,31
X	WO 93 19767 A (UNIV MICHIGAN) 14 October 1993 see page 5, line 20 - page 10, line 30 ---	17-21, 23-29,31
X	WO 95 05464 A (ARCH DEV CORP) 23 February 1995 see page 52, line 20 - line 32 ---	17-19, 22-27, 30,31
X	WO 95 03408 A (DANA FARBER CANCER INST INC ;REPLIGEN CORP (US)) 2 February 1995 see page 57, line 9 - page 58, line 37; claim 170 --- -/--	17-19, 22-27, 30,31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
7 April 1998	20. 05. 1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	**Authorized officer** Fernandez y Branas,F

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CAMERON M.J. ET AL: "Cytokine- and costimulation-mediated therapy of IDDM" CRITICAL REVIEWS IN IMMUNOLOGY, vol. 17, no. 5-6, 1997, pages 537-544, XP002061663 see the whole document	1-31
A	LENSCHOW D.J. ET AL: "CD28/B7 regulation of Th1 and Th2 subsets in the development of autoimmune diabetes" IMMUNITY, vol. 5, no. 3, 1996, pages 285-293, XP002061664 see the whole document	1-31
A	WO 92 00092 A (SQUIBB BRISTOL MYERS CO) 9 January 1992 see the whole document	1-31
A	WO 96 14865 A (REPLIGEN CORP ;DANA FARBER CANCER INST INC (US)) 23 May 1996 see the whole document	1-31
A	WO 94 28912 A (UNIV MICHIGAN ;US GOVERNMENT (US)) 22 December 1994 see the whole document	1-31

INTERNATIONAL SEARCH REPORT

Information patent family members

Intern[illegible] Application No
PCT/CA 98/00015

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9005541 A	31-05-90	CA 2003455 A	23-05-90
		EP 0445228 A	11-09-91
		GR 1001504 B	28-02-94
		IL 92382 A	29-12-94
		JP 4502009 T	09-04-92
WO 9319767 A	14-10-93	AU 684461 B	18-12-97
		AU 4101193 A	08-11-93
		CA 2133075 A	14-10-93
		EP 0637963 A	15-02-95
		JP 7508711 T	28-09-95
WO 9505464 A	23-02-95	AU 7526894 A	14-03-95
WO 9503408 A	02-02-95	AU 7405294 A	20-02-95
		EP 0711345 A	15-05-96
		JP 9500788 T	28-01-97
WO 9200092 A	09-01-92	CA 2086325 A	03-01-92
		EP 0537293 A	21-04-93
		JP 6508501 T	29-09-94
		US 5521288 A	28-05-96
		US 5580756 A	03-12-96
WO 9614865 A	23-05-96	AU 4158396 A	06-06-96
WO 9428912 A	22-12-94	AU 7107794 A	03-01-95

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
RAE, Patricia A.
Sim & McBurney
330 University Avenue
6th floor
Toronto, Ontario M5G 1R7
CANADA

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	21. 10. 98
Applicant's or agent's file reference: 8844-8/PAR	REPLY DUE within 3 months/~~days~~ from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 98/ 00015	12/01/1998	10/01/1997

International Patent Classification (IPC) or both national classification and IPC
A61K38/17

Applicant
THE JOHN P. ROBARTS RESEARCH INSTITUTE et al.

1. This written opinion is the First (first, etc.) drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
   - I [X] Basis of the opinion
   - II [ ] Priority
   - III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 10/05/1999.

Name and mailing address of the IPEA/
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Authorized officer
Examiner Fernández y Brenas, F
01949

Formalities officer
(incl. extension of time limits) C. Cardenas
Telephone No.

I. Basis f the opinion

1. This opinion has been drawn up on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed

☐ the description, pages ,as originally filed

pages ,filed with the demand

pages , filed with the letter of

☐ the claims Nos. ,as originally filed

Nos. ,as amended under Article 19

Nos. , filed with the demand

Nos. , filed with the letter of

☐ the drawings, sheets / fig. ,as originally filed

sheets / fig. , filed with the demand

sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.

☐ the drawings, sheets / fig.

3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

III. **Non- establishm nt of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1- 16

because:

☒ the said international application, or the said claims relate to the following Nos. 1- 16
subject matter which does not require an international preliminary examination
(specify):

Claims 1- 16 relate to a method of treatment of the human or animal body by therapy in the sense of Article 34(4)(a)(i) and Rule 67.1(iv) PCT.

☐ the description, claims or drawings *(indicate particular elements below)* or Nos.
said claims are so unclear that no meaningful opinion could be formed
(specify):

☐ the claims, or said claims are so inadequately supported by the description Nos.
that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive st p r industrial applicability; citations and xplanati ns supp rting such statem nt

1. Statement

Novelty	Claims	17- 31
	Claims	
Inventive Step	Claims	
	Claims	
Industrial Applicability	Claims	17- 31 (see below)
	Claims	

2. Citations and Explanations

D1.....WO- A- 9005541 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN)
D2.....WO- A- 9319767 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN)
D3.....WO- A- 9505464 (ARCH DEVELOPMENT CORPORATION)
D4.....WO- A- 9503408 (DANA- FARBER CANCER INSTITUTE/ REPLIGEN CORP.)
D5.....Immunity, Vol 5, 1996, pages 285- 293

1) For the assessment of the presently worded claims 17- 31 on the question whether their subject matter is industrially applicable, no unified criteria exist in the PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, for example, does not recognise the subject matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for first medical use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2) In the case of a known substance or composition, this may only be patented for use in methods of treatment of the human or animal body if the known substance or composition was not previously disclosed for use in therapy ("first medical use"). The same substance or composition cannot subsequently be patented for any other use of that kind.

3)D1 discloses pharmaceutical compositions comprising anti CD28 agonist antibodies, see for example claims 12- 32; see also D2, page 5 line 20 to page 10 line 30; pharmaceutical

compositions comprising the B7- 2 polypeptide are also known in the art, see D3, page 52, lines 20- 32; see also D4, page 57 line 9 to page 58 line 37 and claim 170.

4) Thus, in view of any of D1- D2 and bearing in mind point 2) above the subject matter of claims 17- 21, 23- 29 and 31 lacks novelty in the sense of Article 33(2) PCT. In view of any of D3- D4 the subject matter of claims 17- 19, 22- 27 and 30- 31 lacks novelty in the sense of Article 33(2) PCT.

5) The IPEA will give an opinion on the novelty and inventive step of the subject matter of claims 1- 16 as if they were drafted in a manner not falling within the meaning of Article 34(4)(a)(i) and Rule 67.1(iv) PCT.

6) In view of the prior art the subject matter of claims 1- 16 appears to be new according to Article 33(2) PCT.

7) For the analysis of the inventive step of the subject matter of claims 1- 16 D5 is considered to be the closest prior art. D5 discloses that administration of CTLA- 4Ig or anti- B7- 2 mAbs blocked diabetes in nonobese diabetic mouse (NOD), when administered to mice between 5 and 7 weeks of age. CTLA- 4Ig Tg^{+} NOD mice and $CD28^{-/-}$ NOD mice displayed a more rapid onset and severity of diabetes . In the later animals, disruption of the CD28/B7 interaction contributed to the exacerbation of the autoimmune disease, see first page, right column. It is concluded that the CD28 signalling pathway controls the development of autoimmune diabetes in NOD mouse by regulating the balance Th1/ Th2 subsets. The blockade of CD28/B7 during the early phase of the T- cell activation contributes to an increase incidence of the disease, see page 290, right column.

The difference between the present application and D5 is that in the present application agonists of the CD28 receptor (e.g. anti CD28 antibodies or the B7- 2 polypeptide) is used in the preparation of medicaments for preventing the development of autoimmune disease. In view of this difference the problem to be solved by the present application can be defined as the provision of alternative medicaments for preventing autoimmune diseases.

Although D5 mentions that disruption of the CD28/B7 interaction contributes to the development of the disease, no clear suggestion can be found in D5 directing the skilled person to the

stimulation of the CD28 receptor with costimulatory agonist compounds. Thus, the subject matter of claims 1- 16 involves an inventive step in the sense of Article 33(3) PCT.

The Applicant is requested to bear in mind that according to Rule 66.4 PCT the issuance of an additional written opinion is facultative. Moreover, as the final action in the PCT- II procedure is an International Preliminary Examination Report and not a decision a violation of the right to be heard cannot exist. The Applicant cannot therefore rely on obtaining a second written opinion before the International Preliminary Examination Report is issued and is requested to answer to this first written opinion in a complete manner.

VIII. Certain observations on the internati nal application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The subject matter of claims 10- 16 is not considered to be supported by the description. No evidence is provided in the present application to show that the claimed methods would work in prolonging acceptance of engrafted tissue (Article 6 PCT).

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

RAE, Patricia A.
Sim & McBurney
330 University Avenue
6th floor
Toronto, Ontario M5G 1R7
CANADA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.04.99
Applicant's or agent's file reference: 8844-8/PAR	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00015	12/01/1998	10/01/1997

Applicant
THE JOHN P. ROBARTS RESEARCH INSTITUTE et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
8844-8/PAR		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA98/00015	12/01/1998	10/01/1997
International Patent Classification (IPC) or national classification and IPC A61K38/17		
Applicant THE JOHN P. ROBARTS RESEARCH INSTITUTE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
23/07/1998	29.04.99
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. (+31-70) 340-2040 Tx: 31 651 epo nl Fax: (+31-70) 340-3016	Authorized officer Fernandez y Branas,F Telephone No. (+31-70)-340

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00015

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-32 as originally filed

Claims, No.:

1-31 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-16.

because:

☒ the said international application, or the said claims Nos. 1-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	17-31
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	17-31
Industrial applicability (IA)	Yes:	Claims	1-31 (See Sep. Sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-16 relate to a method of treatment of the human or animal body by therapy in the sense of Article 34(4)(a)(i) and Rule 67.1(iv) PCT.

The IPEA will nevertheless give an opinion on the novelty and inventive step of the subject matter of claims 1-16 as if they were drafted in a manner not falling within the meaning of Article 34(4)(a)(i) and Rule 67.1(iv) PCT.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1.....WO-A-9005541 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN)
D2.....WO-A-9319767 (THE REGENTS OF THE UNIVERSITY OF MICHIGAN)
D3.....WO-A-9505464 (ARCH DEVELOPMENT CORPORATION)
D4.....WO-A-9503408 (DANA-FARBER CANCER INSTITUTE/ REPLIGEN CORP.)
D5.....Immunity, Vol 5, 1996, pages 285-293

1) For the assessment of the presently worded claims 1-31 on the question whether their subject matter is industrially applicable, no unified criteria exist in the PCT. The patentability under national patent laws can also be dependent on the formulation of the claims. The EPO, for example, does not recognise the subject matter of claims to the use of a compound in medical treatment as being industrially applicable, but will allow, however, claims to a known compound for first medical use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical

treatment.

2) In the case of a known substance or composition, this may only be patented for use in methods of treatment of the human or animal body if the known substance or composition was not previously disclosed for use in therapy ("first medical use"). The same substance or composition cannot subsequently be patented for any other use of that kind.

3)D1 discloses pharmaceutical compositions comprising anti CD28 agonist antibodies, see for example claims 12-32; see also D2, page 5 line 20 to page 10 line 30; pharmaceutical compositions comprising the B7-2 polypeptide are also known in the art, see D3, page 52, lines 20-32; see also D4, page 57 line 9 to page 58 line 37 and claim 170.

4) Thus, in view of any of D1-D2 and bearing in mind point 2) above the subject matter of claims 17-21, 23-29 and 31 lacks novelty in the sense of Article 33(2) PCT. In view of any of D3-D4 the subject matter of claims 17-19, 22-27 and 30-31 lacks novelty in the sense of Article 33(2) PCT.

5) In view of the prior art the subject matter of claims 1-16 appears to be new according to Article 33(2) PCT.

6) For the analysis of the inventive step of the subject matter of claims 1-16 D5 is considered to be the closest prior art. D5 discloses that administration of CTLA-4Ig or anti-B7-2 mAbs blocked diabetes in nonobese diabetic mouse (NOD), when administered to mice between 5 and 7 weeks of age. CTLA-4ig Tg^+ NOD mice and $CD28^{-/-}$ NOD mice displayed a more rapid onset and severity of diabetes . In the later animals, disruption of the CD28/B7 interaction contributed to the exacerbation of the autoimmune disease, see first page, right column. It is concluded that the CD28 signalling pathway controls the development of autoimmune diabetes in NOD mouse by

regulating the balance Th1/ Th2 subsets. The blockade of CD28/B7 during the early phase of the T-cell activation contributes to an increase incidence of the disease, see page 290, right column.

The difference between the present application and D5 is that in the present application agonists of the CD28 receptor (e.g. anti CD28 antibodies or the B7-2 polypeptide) is used in the preparation of medicaments for preventing the development of autoimmune disease. In view of this difference the problem to be solved by the present application can be defined as the provision of alternative medicaments for preventing autoimmune diseases.

Although D5 mentions that disruption of the CD28/B7 interaction contributes to the development of the disease, no clear suggestion can be found in D5 directing the skilled person to the stimulation of the CD28 receptor with costimulatory agonist compounds. Thus, the subject matter of claims 1-16 involves an inventive step in the sense of Article 33(3) PCT.

Re Item VIII
Certain observations on the international application

The subject matter of claims 10-16 is not considered to be supported by the description. No evidence is provided in the present application to show that the claimed methods would work in prolonging acceptance of engrafted tissue (Article 6 PCT).

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published
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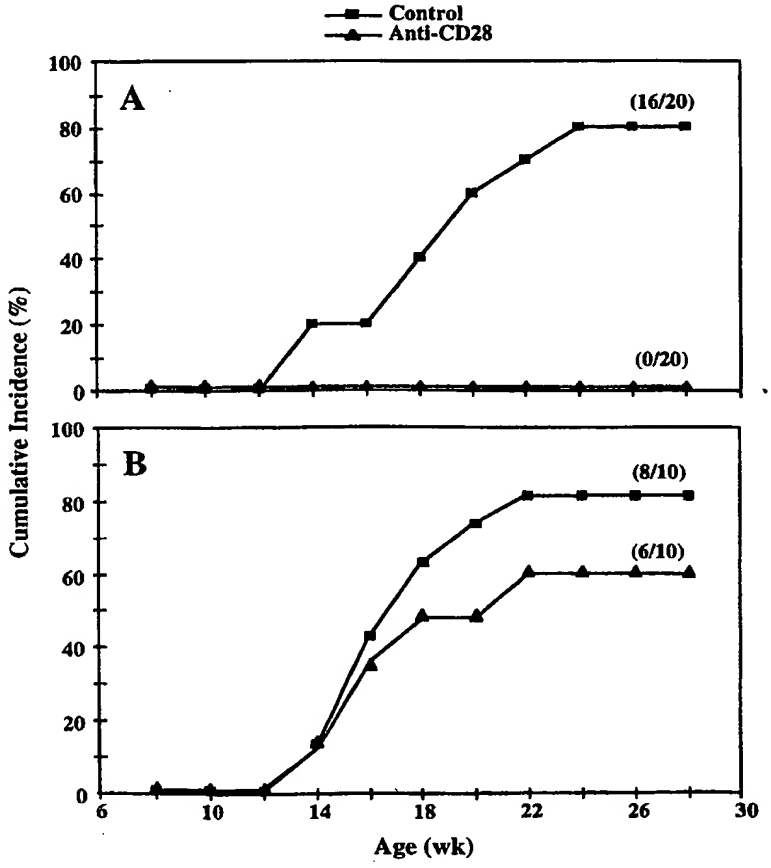
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS AND COMPOSITIONS FOR PREVENTING AUTOIMMUNE DISEASE

(57) Abstract

Methods and compositions are provided for preventing the development of autoimmune diseases in susceptible subjects and for prolonging acceptance of tissue transplants by administration of an agonist of the T cell CD28 costimulatory receptor.



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